## REMARKS

### I. Status of Claims

Applicants have amended claims 1, 4-7, 11, 12, 17, and 22-28, canceled claim 18, and added new claims 29 and 30. Support for the amendments is found, e.g., at page 1, lines 27-28 (BCMA); page 7, lines 19-26 (amino acids 1 to 51 and 8 to 41 of SEQ ID NO:1); page 8, lines 3-11 (95% identity with SEQ ID NO:1), and page 13, line 6 to page 15, line 7 (anti-BCMA antibodies). Upon entry of this amendment, claims 1, 4-7, 11, 12, 17, and 22-30 are pending. Applicants reserve the right to pursue subject matter not covered by the currently pending claims in one or more later filed applications.

### II. Restriction/Election

Applicants affirm election of the claims of Group II (1, 4-7, 11, 12, 17, and 22-28). New claims 29 and 30 are also drawn to the elected subject matter and Applicants request that these claims be examined with the claims of Group II.

### III. Information Disclosure Statement

Applicants attach copies of journal articles cited in the information disclosure statement filed July 12, 2004, for consideration by the Examiner. A new Form PTO-SB-08 is also attached.

## AMENDMENTS TO THE DRAWINGS

Please amend Figures 1, 3, and 7 as indicated on the attached sheets of drawings. Figure 1 is amended to omit the box containing the terms "Figure 2A-2B" from the bottom right corner. Figure 3 is amended to include sequence identifiers. Figure 7 is amended to include a lighter copy of the image, taken from Figure 7 of priority document U.S. Serial No. 60/149,378.

Attachments: Replacement sheets (3 sheets; Figures 1, 3, and 7)

Annotated sheets showing changes (3 sheets; Figures 1, 3, and 7)

## IV. Formal matters

The Examiner objects to Figures 1, 3, and 7 for alleged formal deficiencies. Applicants attach a corrected version of Figure 1 that omits the box containing the terms "Figure 2A-2B" from the bottom right corner. Applicants attach a corrected version of Figure 3 that includes the relevant sequence identifiers. Applicants attach a corrected version of Figure 7 containing a lighter copy of the data, taken from Figure 7 of priority document U.S. Serial No. 60/149,378.

The Examiner objects to the title as allegedly not descriptive. Applicants have amended the specification, changing the title to "METHODS OF TREATMENT BY ADMINISTERING AN ANTI-BCMA ANTIBODY."

The Examiner objects to claims 1, 4-7, and 17 for reciting "BAFF-R" without first defining the term in the independent claims. Applicants have amended the claims to recite "BCMA" as an acronym for "B cell maturation protein." The specification uses the terms "BCMA" and "BAFF-R" interchangeably. See, e.g., page 1, lines 27-28; page 3, lines 25-26; and page 7, lines 6-7. However, since the application was filed, the term "BAFF-R" has come to be used more commonly to refer to a distinct protein that also serves as a receptor to BAFF. Thus, Applicants have amended the claims to recite the term "BCMA" instead of "BAFF-R" so that they are consistent with the most current usage of these terms by those of skill in the art.

The Examiner objects that claim 28 is missing a word after "antibody." Applicants have amended claim 28 accordingly, adding the word "comprises."

In view of the foregoing amendments and remarks, Applicants respectfully request that the objections for alleged formal deficiencies in the sequence listing, drawings, specification, and claims be reconsidered and withdrawn.

## V. Double Patenting

The Examiner has provisionally rejected claims 1, 4-7, 11, 17, and 22 under the doctrine of obvious-type double patenting, in view of claims 1, 2, 7, and 11 of copending Application No. 10/115,192 ("the '703 application").

Applicants respectfully traverse this rejection as it relates to the amended claims, but, at this time, request that this rejection be held in abeyance until allowable subject matter is indicated. At that time, Applicants will consider whether or not to file a Terminal Disclaimer.

## VI. 35 U.S.C. § 112, First Paragraph - Enablement

The Examiner has rejected claims 1, 4-7, 11, 12, 17, and 22-28 under 35 U.S.C. §112, first paragraph, alleging that the claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

Without conceding the Examiner's position, Applicants submit that the amended claims clearly set forth the intended subject matter and that the disclosure enables the full scope of the amended claims.

The test for enablement is whether Applicants' disclosure, coupled with information known in the art, would allow the skilled artisan to make and use the claimed invention without undue experimentation. United States v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988); In re Stephens, 188 USPQ 659 (CCPA 1976). The standard is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 540, 190 USPQ 214, 219 (CCPA 1976). Non-critical features of the invention may be supported by a more general disclosure than those at the heart of the invention. In re Stephens, 188 USPQ 659 (CCPA 1976).

The instant claims relate to methods of inhibiting B-cell growth, immunoglobulin production, or inflammation and methods of treating autoimmune disease, hypertension, renal disorders, or B-cell lympho-proliferate disorders. As amended, the claimed methods comprise administering a therapeutically effective amount of an antibody that specifically binds to (or is immunospecific to an antigenic determinant of) a polypeptide comprising the sequence of SEQ ID NO:1; amino acids 1 to 184, 1 to 51, or 8 to 41 of SEQ ID NO:1; or a sequence that binds to BAFF and is at least 95% identical to amino acids 1 to 184 of SEQ ID NO:1.

As described in more detail below, the results and working examples disclosed in the specification provide a direct demonstration of success in inhibiting B-cell growth and treating autoimmune disease by administering a BCMA-BAFF blocking agent. The skilled artisan would recognize that these results predict success in administering a BCMA-BAFF blocking agent to inhibit immunoglobulin production or inflammation or to

treat renal disorders, B-cell lymphoproliferate disorders, or hypertension, in view of the fact that B cells and/or dendritic cells are involved in each of these disorders. The correlation between the effects of BCMA on B cells and the disorders and conditions recited in the claims is reasonable; therefore the claims are enabled with regard to the conditions treated (MPEP 2164.02). A rigorous or an invariable exact correlation is not required (MPEP 2164.02, citing Cross v. Iizuka, 224 USPQ 739, 747 (Fed. Cir. 1985)).

Applicants respectfully submit that the Examiner's arguments regarding variation in the pathologies of these conditions, B cell stimuli other than BAFF, the question of whether all B cells, or even all lymphocytes, would be inhibited, and an alleged lack of guidance as to which tissues or organs are targeted are inapposite. Office Action, at 7-9. The patent laws do not require that *all* aspects of a pathology be treated, or that a condition be completely cured, for a method of treatment claim to be enabled. The claims do not require treatment of *all* aspects of the pathology of each condition, inhibition of *all* B cell stimuli, inhibition of *all* B cells, or targeting of particular organs. The reasonable expectation of success in treating the recited conditions is based not on any expectation that BCMA-BAFF blocking agents are as omnipotent as the Examiner would seem to require, but on the fact that all of the claimed indications involve misregulation of B cells and/or dendritic cells, and that BCMA can modulate the function of these of cells, as Applicants have shown.

Further, the skilled artisan would know how to make antibodies that specifically bind the polypeptides recited in the claims. The specification provides ample guidance in this regard, including citations of several art publications that teach a variety of

methods for producing and modifying antibodies. See, e.g., page 13, line 6 to page 15, line 7. The specification also includes an example describing "Generation of Agonistic or Antagonistic Antibodies" (Example 6, page 22, lines 13-30). Applicants also note Example 16 of the Patent Office's Synopsis of Interpretation of the Written Description Guidelines, discussed further below with respect to written description. In this Example, the Patent Office recognizes "the routine art-recognized method of making antibodies to fully characterized antigens . . . and the fact that the antibody technology is well developed and mature." Synopsis of Interpretation of the Written Description Guidelines, at 59-60. Between Applicants' disclosure and extensive knowledge of antibodies in the art, the skilled artisan would be well aware of techniques for making the recited antibodies.

Applicants' disclosure also teaches the skilled artisan how to use these antibodies. Applicants teach that agents that block BAFF from binding BCMA can be administered in methods of inhibiting B-cell growth, immunoglobulin production, or inflammation and methods of treating autoimmune disease, hypertension, renal disorders, or B-cell lympho-proliferate disorders (page 1, lines 10-25 and page 16, lines 7-20). These teachings are supported by Examples 8, 9, 11, 13, and 14, which present a variety of experiments demonstrating that inhibiting BAFF from binding to BCMA by administering a soluble BCMA-IgG fusion blocks BAFF-induced B cell proliferation in vitro (page 26, line 22, to page 27, line 22), reduces the number of B cells in vivo (page 23, line 11, to page 26, line 20), attenuates lupus-like disorders (page 28, line 24, to page 32, line 31), slows progression of lupus nephritis (page 34, lines 1-18), and causes

reduction and mislocalization of splenic dendritic cells (page 34, line 20, to page 36, line 7). Further, Example 12 shows that BAFF transgenic mice have a tendency towards hypertension, and teaches that administering a soluble BCMA, fusion protein, or antibody can ameliorate the effects of hypertension (page 33, lines 1-30).

These results provide a direct demonstration of success in inhibiting B-cell growth and treating autoimmune disease by administering a BCMA-BAFF blocking agent. The skilled artisan would also recognize that these results predict success in administering a BCMA-BAFF blocking agent to inhibit immunoglobulin production or inflammation or to treat renal disorders, B-cell lymphoproliferate disorders, or hypertension, in view of the fact that B cells and/or dendritic cells are involved in each of these disorders.

The skilled artisan would also understand that antibodies against BCMA are alternatives to soluble BCMA fusions. See, e.g., page 1, lines 10-25, which refers to the therapeutic applications of "blocking agents, such as recombinant variants or antibodies specific to the receptor." Indeed, Applicants teach that antibodies are not only alternatives to BCMA-Ig fusions, but antibodies can actually be more effective blocking agents. "Antibodies to the receptor can block ligand binding and hence also have clinical applications. Such antibodies are often very long-lived and may have advantages over soluble receptor-Ig fusion proteins which have shorter blood half-lives" (page 2, line 31, to page 3, line 3). In view of these teachings and the demonstrated success of methods comprising administration of BCMA-IgG, the skilled artisan would

expect at least similar, or even better, results using antibodies that bind to BCMA in the claimed methods.

Applicants respectfully submit that the Examiner's argument regarding the lack of working examples that indicate an anti-BCMA antibody is effective in the claimed methods is improper. Office Action, at 7. As an initial matter, Applicants note that working examples are not required. In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Further, Applicants note again that the disclosure does include several working examples of administration of a BCMA-Ig fusion and teaches that an antibody that binds BCMA is an alternative blocking agent that may actually be a more effective therapeutic agent than the BCMA-Ig fusion due to the longer physiological half-life of antibodies.

The Examiner also alleges that problems were often encountered when attempting to use antibodies as clinical reagents, pointing to the human response to foreign antibodies, low affinity or nonoptimal systemic half-life of antibodies, and difficulty producing sufficient quantities of antibody for therapy. Office Action, at 9-10. However, Applicants' disclosure specifically addresses these considerations and provides remedies for each. The patient's immune response against the administered antibody may be reduced, for example, by constructing chimeric antibodies, humanized antibodies, or antibody fragments (page 13, line 30, to page 14, line 25). Affinities may be increased by altering amino acids in or near the antigen binding site (page 15, lines 3-7). Antibodies may be produced by standard recombinant techniques (page 14, lines

9-11). Further, the skilled artisan would understand that a routine aspect of practicing any method involving an antibody is considering and often testing such characteristics.

Applicants also note that numerous antibody therapeutics are currently on the market or in late stage clinical trials, illustrating that antibody therapeutics can be effective. The fact that an antibody against the TNF ligand (infliximab) had been successfully used in Phase III clinical trials for the treatment of rheumatoid arthritis as early as 1999 specifically supports the use of antibodies to disrupt signaling by members of the TNF superfamily. Maini, et al., Lancet 354:1932-39 (1999). Further, the Maini article, which was published in 1999, is more indicative of the state of the art as of the priority date than the 1989 and 1997 publications cited by the Examiner.

Thus, in view of Applicants' disclosure and the level of skill in art, routine considerations of antibody production and optimization would not cause the skilled artisan to question the enablement of the claimed methods.

With the skilled artisan thus fully expecting success in using antibodies against BCMA, Applicants' disclosure and routine knowledge in the art would also allow the skilled artisan to administer these antibodies in the claimed methods without undue experimentation. The specification teaches that "administration may be accomplished by injection (eg intravenous, intraperitoneal, subcutaneous, intramuscular) or by other methods such as infusion that ensure delivery to the bloodstream in an effective form" (page 17, lines 3-5). Examples 8, 9, 11, 13, and 14, discussed above, provide additional guidance as to possible modes of administration, dosage, duration of treatment, etc.. The skilled artisan would understand how to conduct any routine

experiments needed to optimize the exact conditions of administration. Applicants note again that non-critical features of the invention may be supported by a more general disclosure than those at the heart of the invention. In re Stephens, 188 USPQ 659 (CCPA 1976).

The combination of Applicants' disclosure and routine knowledge in the art would thus allow the skilled artisan to envision the encompassed polypeptides, understand how to make the corresponding antibodies, know that a BAFF-BCMA blocking agent successfully inhibits B cell growth and treats disorders of the immune system, appreciate that antibodies against BCMA are alternatives, and perhaps superior, to BCMA-Ig fusions, and realize how to administer antibodies against BCMA in the claimed methods. In short, the skilled artisan would know how to make and use the invention without undue experimentation. Accordingly, Applicants respectfully request that the rejection for alleged lack of enablement be withdrawn.

## VII. 35 U.S.C. § 112, First Paragraph - Written Description

The Examiner has rejected claims 1, 4-7, 11, 12, 17, and 22-28 as allegedly failing to meet the written description requirement of 35 U.S.C. § 112, first paragraph. The Examiner states that the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides or the antibodies that bind to these polypeptides, citing Fiers v. Revel, 25 USPQ2d 1601 at 1606 (Fed. Cir. 1993), Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016, and Fiddes v. Baird, 30 USPQ2d 1481 at 1483.

Without conceding the Examiner's position, Applicants have amended the claims to more clearly set forth the intended subject matter. Applicants respectfully submit that the amended claims are adequately described.

The amended claims recite antibodies that specifically bind to polypeptides consisting of the sequence of SEQ ID NO:1; amino acids 1 to 184, 1 to 51, or 8 to 41 of SEQ ID NO:1; sequences that bind to BAFF and are at least 95% identical to amino acids 1 to 184 of SEQ ID NO:1; and antibodies that are immunospecific to an antigenic determinant of a polypeptide consisting of SEQ ID NO:1. As amended, the claims define the detailed chemical structure of the targeted polypeptides narrowly by reference to specifically disclosed sequences. Therefore, this is a completely different situation than that addressed by the Fiers v. Revel line of cases. The amended claims satisfy the written description requirement under the Office's own guidelines. In particular, the examiner is directed to Examples 14 and 16 of the Synopsis of Interpretation of the Written Description Guidelines. Example 14 concludes that a single polypeptide sequence is sufficiently representative of a genus of polypeptides "at least 95% identical" to the specified sequence when the genus is also limited by a functional characteristic, as is the case for claim 11. Example 16 concludes that a claimed genus of antibodies which is limited solely by the functional limitation, "capable of binding to antigen X" is adequately described in view of the disclosure of antigen X and the extensive knowledge in the art regarding antibody structure and function, as well as of methods of making antibodies against fully characterized antigens.

The Federal Circuit discussed and approved of this standard for written description of antibodies in *Noelle v. Lederman* , 355 F.3d 1343 (Fed. Cir. 2004), discussing *Enzo Biochem. v. Gen-Probe, Inc.*, 323 F.3d 956, 63 U.S.P.Q.2d 1609 (Fed. Cir. 2002). In view of these clear structural and functional limitations and the corresponding disclosures, the skilled artisan would immediately comprehend the encompassed polypeptides and antibodies.

Accordingly, Applicants submit that the amended claims satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, and respectfully request that this rejection be withdrawn.

## VIII. 35 U.S.C. § 112, Definiteness

The Examiner has rejected to claims 23-28 as allegedly lacking antecedent basis for "anti-BAFF antibody." Claim 23 is now independent, and amended claims 24-28 refer to "the antibody" of claim 1, 4, 5, 6, 7, 11, or 23. Accordingly, Applicants respectfully request that this rejection be withdrawn.

## IX. Priority

The Examiner has denied Applicants' claims for priority to 60/149,378, 60/181,684, and 60/183,536, and PCT/US00/22507, alleging that these provisional applications do not provide adequate support under 35 U.S.C. §112, first paragraph for claims 1, 4-7, 11-12, 17-18, 22-28.

Without conceding the Examiner's position with respect to the previously pending claims, Applicants respectfully request that the Examiner reconsider the priority date with regard to the amended claims. Applicants note that the Examiner has acknowledged that the "polypeptide of SEQ ID NO:1 and antibodies that bind the polypeptide of the instant application are fully disclosed in the prior applications." Office Action, at 16.

With respect to the earliest priority claim, exemplary support for the amended claims is found in Application Serial No. 60/149,378, including at least at page 1, lines 1-13 and page 15, lines 12-25 (methods of inhibiting B-cell growth, immunoglobulin production, or inflammation; methods of treating autoimmune disease, hypertension, renal disorders, B-cell lympho-proliferate disorders); page 6, lines 10-11 (amino acids 1 to 51 of SEQ ID NO:1); page 7, lines 15-18 (amino acids 1 to 184 of SEQ ID NO:1); page 7, line 23 (amino acids 8 to 41 of SEQ ID NO:1); page 8, lines 4-7 (sequences having at least about 80, 85, 90, or 95 percent identity with SEQ ID NO:1); page 11, lines 18-30 (BCMA fragments); page 12, lines 1-12 (soluble BCMA); page 12, lines 14-28 (antibodies that bind to BCMA, including monoclonals and antibodies that are immunospecific for antigenic determinants of BCMA); page 13, lines 6-30 (F(ab)2 fragments, human clinical treatments, and recombinant, humanized, or chimeric antibodies); and page 14, lines 3-6 (antibodies comprising human constant domains).

Accordingly, Applicants respectfully submit that the amended claims are entitled to the earliest claimed priority date, August 17, 1999, and request that the claims for priority under 35 U.S.C. § 119(e) and 35 U.S.C. § 120 be granted.

## X. 35 U.S.C. §§ 102 and 103

### A. Gross et al., WO/00/40716

The Examiner has rejected claims 1, 4-7, 11-12, 17-18, 22-25 under 35 U.S.C. §102(b) as allegedly anticipated by WO/00/40716 ("the '716 application"). Claim 26 has been rejected under 35 U.S.C. §103(a) as allegedly obvious over the '716 application in view of Colcher et al., Q. J. Nucl. Med 43:132-139 (1999). In view of the foregoing remarks with respect to priority, Applicants submit that the instant application is entitled to the earliest priority date of August 17, 1999. Thus, without comment as to the allegation that claims read on or are obvious in view of the '716 application, Applicants submit that the instant application predates the reference, which is only effective as of its July 13, 2000, publication date. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. §102(b) and 35 U.S.C. §103(a) be withdrawn.

### B. Shu et al., U.S. Patent No. 6,475,987

Claims 1, 4-7, 11-12, 17-18, and 22-27 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 6,475,987 ("the '987 patent"). Claim 28 has been rejected under 35 U.S.C. §103(a) as allegedly obvious over the '987 patent in view of Colcher et al., Q. J. Nucl. Med 43:132-139 (1999). In view of the foregoing remarks with respect to priority, Applicants submit that the instant application is entitled to the earliest priority date of August 17, 1999. Thus, without comment as to the allegation that the claims read on or are obvious in view of the '987 patent, Applicants submit that

the instant application predates the reference, which issued November 5, 2002 and was filed May 5, 2000 (without acquiescing as to the priority date to which the '987 patent is entitled, Applicants note that the Examiner states that this reference has the benefit of priority to May 1, 2000). Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. §102(e) and 35 U.S.C. §103(a) be withdrawn.

## XI. Conclusion

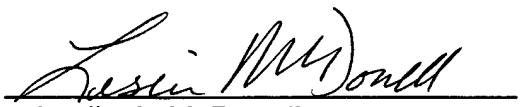
In view of the foregoing amendments and remarks, Applicants respectfully submit that all outstanding rejections have been overcome. Accordingly, Applicants earnestly request reconsideration and expedited allowance of the claims. The Examiner is urged to call the undersigned with any questions at (617) 452-1650.

Applicants believe that any fee required for the entry of this Amendment and Response is accounted for by the accompanying Petition for Extension of Time. However, in the event of an error, please grant any additional extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: August 8, 2005

By: 

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         101▶ N   I   D   L   E   K   S   R   T   G   D   E   I   I   L   P   R   G   L   E
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         161▶ T   N   D   Y   C   K   S   L   P   A   A   L   S   A   T   E   I   E   K   S
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FIG. 1

1/19

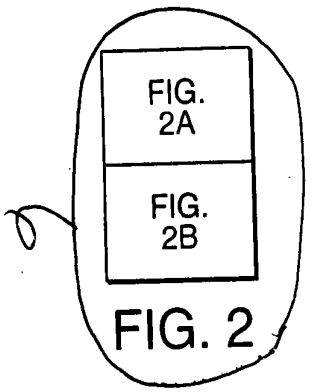
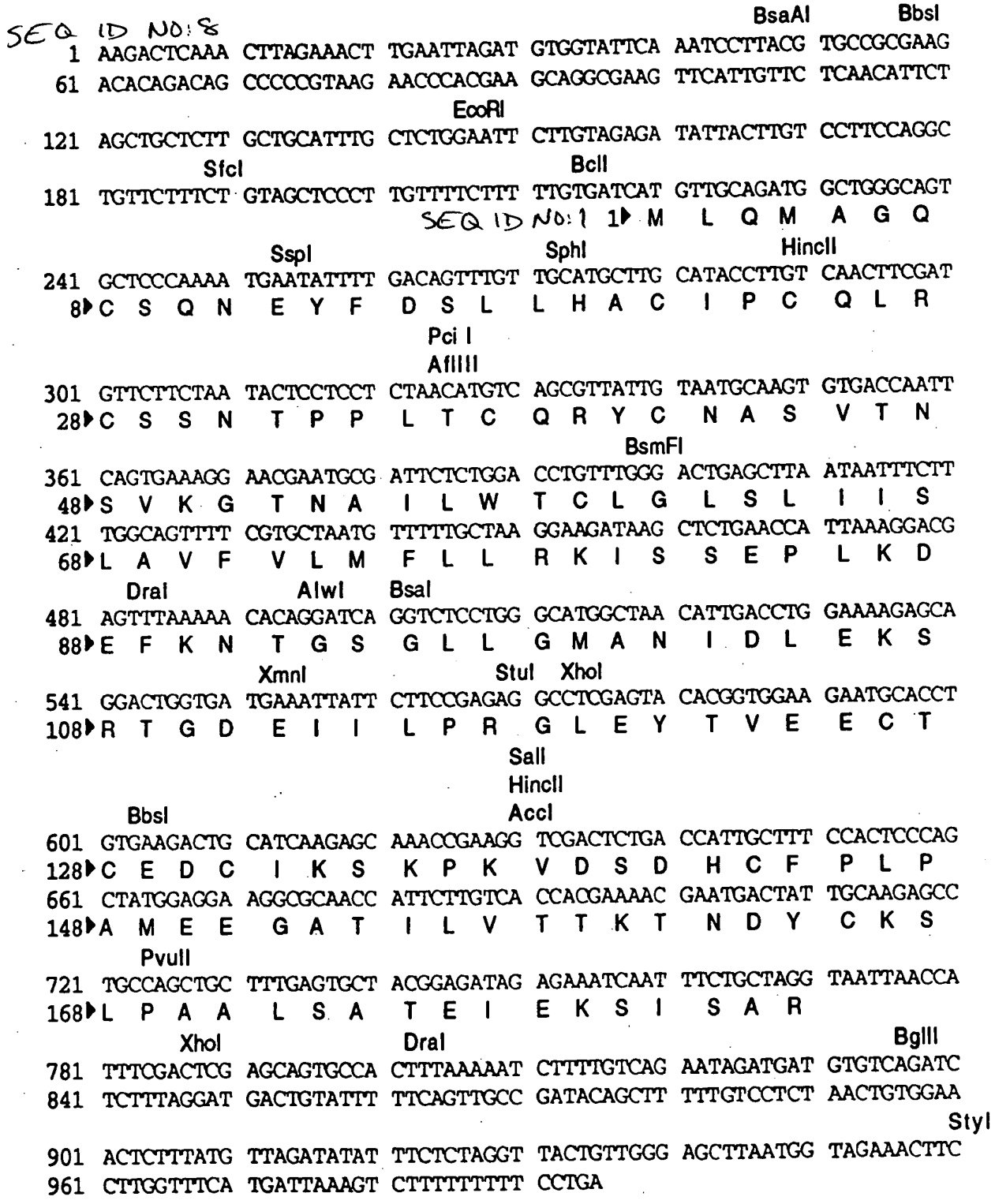



FIG. 2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Pci I
AflIII
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28 C S S N T P P L T C Q R Y C N A S V T N
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361 CAGTGAAAGG AACGAATGCG ATTCTCTGGA CCTGTTTGGG ACTGAGCTTA ATAATTTCTT
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421 TGGCAGTTTT CGTGCTAATG TTTTTGCTAA GGAAGATAAG CTCTGAACCA TTAAAGGACG
68 L A V F V L M F L L R K I S S E P L K D
DraI
AlwI
BsaI
481 AGTTTAAAAA CACAGGATCA GGTCTCCTGG GCATGGCTAA CATTGACCTG GAAAAGAGCA
88 E F K N T G S G L L G M A N I D L E K S
XmnI
StuI
XhoI
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108 R T G D E I I L P R G L E Y T V E E C T
SalI
HincII
AccI
BbsI
601 GTGAAGACTG CATCAAGAGC AAACCGAAGG TCGACTCTGA CCATTGCTTT CCACTCCCAG
128 C E D C I K S K P K V D S D H C F P L P
661 CTATGGAGGA AGGCGCAACC ATTCTTGTCA CCACGAAAAC GAATGACTAT TGCAAGAGCC
148 A M E E G A T I L V T T K T N D Y C K S
PvuII
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XhoI
DraI
BglII
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StyI
901 ACTCTTTATG TTAGATATAT TTCTCTAGGT TACTGTTGGG AGCTTAATGG TAGAAACTTC
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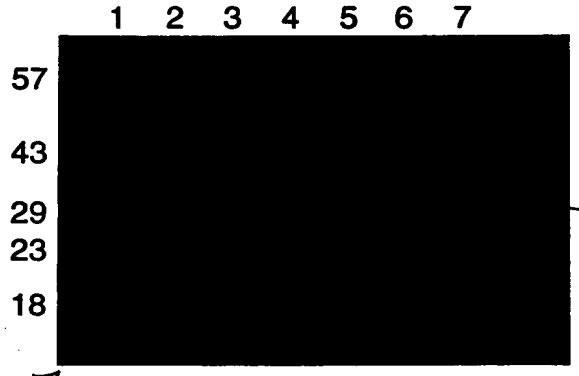
FIG. 3

ANNOTATED SHEET






Bad photocopy replaced with lighter image taken from Fig. 7 of U.S. Serial No. 60/149,378.

FIG. 7

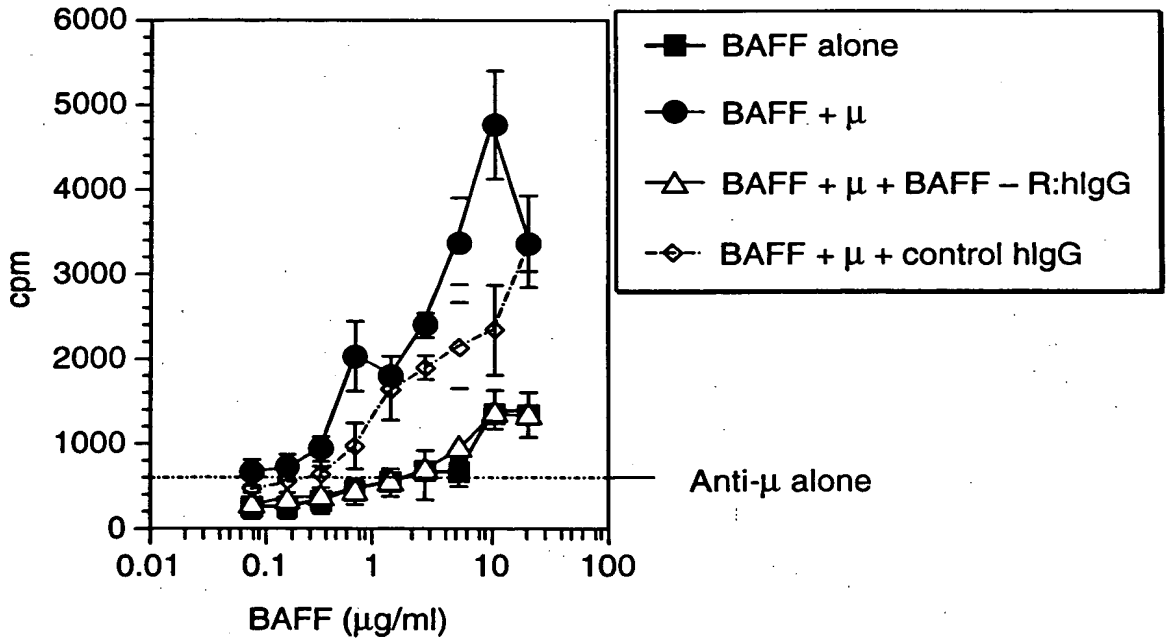



FIG. 8